REMARKS

Upon entry of the forgoing amendment, claims 1 and 3-6 are pending in the application, with claims 9, 11, 12, 15, and 21-46 withdrawn by the Examiner under 37 C.F.R. § 1.142(b). In anticipation of allowance, claims 2 and 7-48 have previously been canceled without prejudice to, or disclaimer of, the material contained therein. Claims 1 and 3-6 were rejected under 35 U.S.C. § 103.

Applicants have not amended the claims, but provide a copy of the claims as currently pending in accordance with 37 CFR § 1.121.

The Rejection of Claims Under 35 U.S.C. § 103, Is Traversed Or Rendered Moot

The Examiner rejected the claims under 35 U.S.C. 103(a) as unpatentable over Brennan et al., US Patent Publication US 2003/0140361 (hereinafter "Brennan") in view of Yang et al, Science, 1999, 286:525-528 (hereinafter "Yang"), Bell et al., 1999, J. Exp. Med., 190:1417-1425 (hereinafter "Bell"), Kleeff et al., Int. J. Cell, 1999, 81:650-657 (hereinafter "Kleeff") and Friberg et al., Int. J. Cancer, 2002, 101:151-155 (hereinafter "Friberg").

Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness. The Federal Circuit has stated that "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Motorola, Inc. v. Interdigital Technology Corp.*, 43 U.S.P.Q. 2d 1481, 1489 (Fed. Cir. 1997) (quoting *Beckman Instruments, Inc. v. LKB Produkter AB*, 13 U.S.P.Q. 2d 1301, 1304 (Fed. Cir. 1989)). Also, subsection 706.02(j) of the MPEP states that to establish a prima facie case of obviousness three criteria must be met:

(i) a suggestion or motivation to modify or combine references;

(ii) a reasonable expectation of success; and

(iii) all the limitations in the claim(s) must be taught or suggested by the reference, or combination of references.

Applicants respectfully assert that the combination of the cited references does not enable one skilled in the art to make and use Applicants' invention, nor do the

references describe, teach or suggest all of the limitations of Applicants' claimed invention.

Applicants claim a method to reduce recruitment of IDO+ dendritic cells that inhibit T-cell proliferation to at least one of a tumor or a tumor-draining lymph node in a subject, comprising administering a composition comprising an antibody to CCR6 to the subject to reduce recruitment of the IDO+ dendritic cells to the at least one of a tumor or a tumor-draining lymph node, wherein the IDO+ dendritic cells express CCR6 and elevated levels of indoleamine 2,3-dioxygenase (IDO), and tumor cells of the at least one of a tumor or a tumor draining lymph node express MIP-3α. Thus, the claims require inhibition of recruitment of IDO+ dendritic cells that express CCR6. As indicated below, the references cited by the Examiner, do not describe, teach or suggest that IDO+ dendritic cells express CCR6, and/or that the migration of IDO+ dendritic cells can be inhibited by anti-CCR6 antibodies.

First, the Examiner cites Brennan as describing that CCR6 antibodies can be used to inhibit CCR6 activity. Office Action at page 3-4. Brennan does not actually provide such antibodies, but merely describes that anti-CCR6 antibodies can be made for detection of the CCR6 gene product or may antagonize CCR6 activity. In contrast to Applicants, Brennan is concerned with methods to generate an animal or animal cells with a disruption in the CCR6 gene. Also, Brennan is concerned with the identification of agents that interact with processes modulated by CCR6, and claims method to treat inflammatory conditions dependent on CCR6, such as inflammatory bowel disease, Chron's disease, rheumathoid arthritis or asthma by treating with agents that are CCR6 agonists, as opposed to CCR6 antagonists. Brennan does not, however, address the use of anti-CCR6 antibodies as a way to prevent migration of CCR6-expressing cells, or as a means to prevent the migration of IDO+ dendritic cells to cancer. Nor does Brennan describe, teach or suggest the use of antagonists of CCR6 as anti-cancer therapeutics. Thus, one of skill in the art would not look to the teachings of Brennan as suggesting Applicants' claimed invention.

The Examiner cites Yang as describing that defensins are chemotactic for immature dendritic cells ("DCs"), and that beta-defensins are selectively chemotactic for cells stably transfected to express human CCR6. Office Action at page 4. However, Yang

only focuses on DC migration in response to beta-defensins. There is no description that the DCs having migration induced by beta-defensin are a population of DCs that express IDO (i.e., an IDO+ subpopulation). As discussed in the specification, Applicants and others have shown that specific signaling is required for induction of IDO expression in DCs. There is no evidence that the immature DCs of Yang would have be subjected to the proper intracellular and intercellular signaling required for induction of IDO+. In fact, Yang specifically states that mature DCs, which express the markers CD1a, CD83, CD86, and HLA-DR (i.e., CD1a+, CD83+, CD86+ and HLA-DR+) did NOT migrate in response to human beta-defensin. Yang at 526, second column. This is in contrast to Applicants' findings indicating that CCR6 and IDO are expressed on differentiated, matured DCs. See the specification at pages 21-22 providing a model for IDO expression. Also, see the specification at page 23, lines 13-24, noting that specific maturation agents may be used to induce IDO expression. As discussed in Applicants' specification, it is desired to specifically prevent the migration of IDO+ DCs to tumors, as such cells are generally immunosuppressive. Applicants' specification provides the finding that CCR6 is expressed on mature DCs that express IDO (i.e., IDO+ DCs). Reading Yang, without the benefit of Applicants' specification, one would NOT be motivated to use anti-CCR6 antibodies to try and prevent the migration of IDO+ DCs to tumor sites as: (1) based on Yang, there is no indication that migration of mature IDO+ DCs to a tumor site would be inhibited; and (2) Yang does not provide any indication that CCR6+ DCs would express IDO.

The Examiner cites Bell as describing that immature dendritic cells can be found in tumors, that CCR6 is expressed on immature DCs, and that mip-3α on tumor cells may attract immature dendritic cells to the mip3α-expressing tumor. Office Action at page 5. Again, there is no description in Bell that the immature DCs infiltrating the tumor are a population of DCs that express IDO (i.e., an IDO+ subpopulation). Bell describes that the immature DCs recruited to tumors express CD1a+. See Bell at Abstract.[1] Bell specifically describes, however, that DCs matured by CD40 ligation do not migrate to the tumor, but remain in peritumoral areas. Bell at page 1422, second column. As discussed above, Applicants have shown that specific differentiation and/or maturation factors may

[1] This is in contrast to Yang, which indicates that mature DCs express CD1a.

be required for induction of IDO expression in DCs. There is no evidence in Bell that the immature DCs found at the tumor sites would have be subjected to the proper intracellular and intercellular signaling required for induction of IDO, so as to be responsible for tumor-specific immunosuppression. For example, in contrast to the teachings of Bell stating that DCs matured by CD40 ligation do not migrate to tumors, Applicants have found that in the presence of appropriate differentiation factors, cells treated with maturation agents such as CD40 ligand, TNF-alpha, IL10, TGF-beta express IDO. See the specification at page 23, 17-24. Thus, Applicants respectfully assert that Bell teaches away from Applicants' invention. Reading Bell, one would not necessarily expect that reduction of migration of CCR6-expressing DCs would be of use in terms of reducing immunosupression, as Bell only indicates that migration of any immature DC that expresses CCR6, regardless of the status of IDO+ expression, may be inhibited using anti-CCR6 antibodies. Also, Bell does not address prevention of infiltration of mature DCs that may co-express CCR6 and IDO+ to a tumor site. Because Bell teaches away from Applicants' method, Applicants respectfully assert that Bell should not be cited against Applicants' claimed invention.

The Examiner cites Kleeff as describing that cancer cells express MIP-3α and CCR6. Office Action at page 5. Applicants respectfully assert that Kleeff also teaches away from the use of anti-CCR6 antibodies as an agent to prevent migration of DCs, as reading Kleeff, one would expect anti-CCR6 antibodies to interact directly with the tumor cells and thus, one would not be motivated to use the same antibody as a means to mediate DC migration. Thus, Kleeff does not describe, teach or suggest the use of anti-CCR6 antibodies as a way to prevent migration of CCR6-expressing cells, or as a means to prevent the migration of IDO+ dendritic cells to cancer. Because Kleeff teaches away from Applicants' method, Applicants respectfully assert that Kleeff should not be cited against Applicants' claimed invention.

Finally, Friberg is cited by the Examiner as describing that IDO can be expressed by immune cells that invade tumors, and that such IDO expression may provide the basis for tumors to evade rejection of the tumor. Office Action at pages 5-6. However, Friberg does not describe, teach or suggest that CCR6 expression is associated with IDO

expression so as to define a particular subset of DCs that are CCR6+ and immunosuppressive.

Thus, Applicants respectfully assert that there is no indication that the cells taught by Bell are the same cells described by Yang and/or Friberg. Also, there is no indication that the cells of Bell and Yang express elevated levels of IDO+ or that the cells of Friberg express CCR6. Applicants note that the markers used in each of Bell, Yang and Friberg are different. Yang specifically states that mature DCs, which express the markers CD1a, CD83, CD86, and HLA-DR (i.e., CD1a+, CD83+, CD86+ and HLA-DR+) did NOT migrate in response to human beta-defensin. Bell used CD1a+ and $CD1a^{low}$ to differentiate immature DCs (described as being $CD1a^{+}$) from mature DCs ($CD1a^{low}$) and specifically stated that mature DCs (i.e., that do not express CD1a) are not found in tumors. Thus, it appears that the cells of Yang and Bell are not the same. Also, the *in situ* phenotyping carried out by Bell does not allow for determination of whether the markers are co-expressed in the same cell, so the only information provided is the phenotyping of the tumor. See Table II of Bell. In Bell, some patients had cells that were CD1a+, or CD83+ or CD11c+, or HLA-DR+ or CD80+ or CD86+. However, there is no indication in Bell that the DCs were CD11c+ and/or CD123+ as shown in Applicants' specification. Nor do the other references characterized the cells as being IDO+ and CCR6+ (as well as CD123+, CD11c+) as shown by the Applicants. It is only with the hindsight of Applicants specification, showing that IDO+ and CCR6 is expressed on IDO+ DCs, and that because of the level of CCR6 expression, anti-CCR6 antibodies can interact with such cells to prevent migration, that the method of Applicants invention is enabled.

Thus, Applicants respectfully assert that the references do not, alone, or in combination, describe, teach or suggest that dendritic cells that are IDO+ are also CCR6+. Without this showing, there is no basis to use anti-CCR6 antibodies to prevent recruitment of IDO+ cells to tumors as is described and claimed by Applicants. For at least these reasons, Applicants respectfully request that the rejection of the claims as obvious under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, each of the claims remaining in the application is in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections. The Examiner is respectfully invited to telephone Cynthia B. Rothschild at (336) 747-7541 to discuss any questions relating to the application.

Respectfully submitted,

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N. Dean Powell, Jr. (58,909) for
Cynthia B. Rothschild (Reg. No. 47,040)

KILPATRICK STOCKTON LLP
1001 West Fourth Street
Winston-Salem, North Carolina 27101-2400
Phone: (336) 747-7541
Facsimile: (336) 607-7500